PEPTIDE MIMICS OF THE CYTOKINE RECEPTOR COMMON GAMMA CHAIN
AND METHODS AND COMPOSITIONS FOR MAKING AND USING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to Provisional
5 Application Number 60/036,941 filed February 7, 1997, which is
incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to molecules which have
structures and functions that mimic the gamma chain that is
10 shared by several cytokine recpetors. The present invention
relates to the use of such molecules to modulate cytokine
activity and cytokine mediated functions.

BACKGROUND OF THE INVENTION

A family of related cytokine receptors including the
15 receptors for IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 have been
reported to share a common protein chain, the γ-chain, for
maximal ligand induced receptor binding and signaling. The γ-
chain is a member of the cytokine receptor superfamily which
includes receptors for growth hormone, erythropoietin, IL-3,
20 IL-2, IL-4, IL-7, IL-6 and GM-CSF. The γ-chain is a 64 kd
protein with a fibronectin type II and CKR-SF domain which
share structural homology.

The crystal structure of the human growth hormone
receptor has been published by deVos A.M., et al. 1992 Science

255:306-312, which is incorporated herein by reference, and
shows that the receptors form a homodimer to bind ligand and
induce a signal. The receptors for IL-4 have been shown to be
in the form of a heterodimer consisting of IL-4α and the common

5   γ-chain. A model for the human IL-4:IL-4-Receptor interaction
has been published by Gustchina, A. *et al.* 1995 *PROTEINS:
Structure, Function and Genetics* 21:140-148, which is
incorporated herein by reference.

          Cytokine:receptor complexes are very important

10 mediators of many immune responses. For example, T cell growth
and differentiation is regulated in part by IL-2, IL-4, IL-7,
IL-9, and IL-15. These cytokines have also been reported to
play a role in other immunological functions as well.

          Without the γ-chain, the cytokine receptors which

15 normally form complexes with the γ-chain are much less
efficient in binding their ligands and thus transmitting their
signals to the target cells. Evidence for the central role of
the γ-chain includes the findings that mutations in this
receptor have been demonstrated to be the causative factor in

20 the development of severe combined immunodeficiency. Recently,
Boussiotis, V.A. *et al.* 1994 *Science* 266:1039-1047, which is
incorporated herein by reference, demonstrated that the
development of T cell anergy can be abrogated by signaling
through this receptor by various means.

25   The function and activity of cells of the immune
system are regulated and directed by cytokine:receptor
interactions as is signaling which induces growth and
proliferation. The activation of T cells and B cells is
regulated by cytokine:receptor interactions including

30 cytokine:receptor interactions involving receptors which
include the γ-chain in a heterodimer.

          There is a need for pharmaceutical compositions which
can effectively inhibit the immune responses mediated by
cytokine:receptor interactions. There is a need for a method

35 of inhibiting cytokine mediated cell activation, function,
growth and/or proliferation. There is a need for
pharmaceutical compositions which can effectively inhibit

signaling that involves receptors which include the γ-chain.
There is a need for compositions and methods which can inhibit
or suppress immune responses in order to therapeutically or
prophylactically treat individuals who have conditions,
5   diseases or disorders involving immune abnormal or undesirable
immunological activity.

SUMMARY OF THE INVENTION
        The present invention relates to peptide mimics of the
loops on the γ-chain which either interact with cytokines or
10   the partners of the γ-chain in heterodimeric cytokine receptors
that include the γ-chain.   The peptides of the present
invention are based on human and murine γ-chain sequences.   The
sequences homology for the human and murine γ-chain is high
(71% identical and 82% similar) making the translation from one
15   species to the next more direct.
        The peptide mimics bind to the cytokine or partner
receptor and inhibit cytokine activity.   Inhibitors of the
common γ-chain inhibit the function of IL-2, IL-4, IL-7, IL-9,
IL-13 and IL-15 by preventing their binding to their respective
20   receptors.   Thus, the inhibition of these cytokine mediated
events leads to immuno-suppressive responses which are
beneficial for the prevention or treatment of numerous auto-
immune diseases and graft rejection following various types of
transplant procedures as well as diseases associated with
25   hyperproliferation of T cells and/or B cells.   For example,
many lymphomas are dependent on some of these cytokines (IL-2
for T cell lymphomas and IL-4 for B cell lymphomas) for growth.
        The present invention relates to peptides that consist
of 5 to 25 amino acids including: SEQ ID NO:1 IQLYQTF, SEQ ID
30   NO:2 IHLYQTF, SEQ ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID
NO:5 CLQYLT, SEQ ID NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID
NO:8 CLEHLTQ, SEQ ID NO:9 PIAGSSQQ, SEQ ID NO:36 PICGSSQQ, SEQ
ID NO:10 PLCGSAQH, SEQ ID NO:11 PLAGSAQH, SEQ ID NO:12
NHEPRFLS, SEQ ID NO:13 DYRHKFSL, SEQ ID NO:14 LNLQNL, SEQ ID
35   NO:15 LKLQNL, SEQ ID NO:16 NLSESQL, SEQ ID NO:17 KLSEQL or such

an amino acid sequence with one or more conservative substitutions, wherein the peptide inhibits cytokine mediated signal transduction.

5   The peptides of the invention preferably have constrained conformations and most preferably are cyclic. In preferred embodiments, cysteine residues are provided at the termini of the peptides to form di-sulfide bonds which result in the formation of cyclic peptides.

10   According to some embodiments of the present invention, peptides are selected from the group consisting of: SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19 CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID NO:24 CLQYLTQC, SEQ ID NO:25 CLEHLTQC, SEQ ID NO:26 CPIAGSSQQC, SEQ ID NO:37 CPICGSSQQC, SEQ ID NO:27

15   CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC, SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC, SEQ ID NO:32 CLKLQNLC, SEQ ID NO:33 CNLSESQLC, SEQ ID NO:34 CKLSESQLC and derivative peptides thereof. The derivative peptides consist of amino acid sequences which contain one or more conservative

20   substitutions.   Conservative substitutions include the following:

I may be substituted with V, A or L;
Q may be substituted with N;
L may be substituted with V, A or I;
25   Y may be substituted with F;
V may be substituted with I, A or L;
S may be substituted with T;
A may be substituted with V, I or L;
N may be substituted with Q;
30   E may be substituted with D;
F may be substituted with Y;
D may be substituted with E; and
I may be substituted with V, A or L.

In some preferred embodiments, the V in sequences SEQ
35   ID NO:3 CLQYLV and SEQ ID NO:4 CLEHLV are substituted with T to improve solubility in aqueous solutions. Accordingly,

peptides SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID
NO:24 CLQYLTQC and SEQ ID NO:25 CLEHLTQC are provided.

　　　　The peptides of the invention are derived from
sequences of the murine or human cytokine receptor common gamma
5　chain.

　　　　The peptides correspond to murine cytokine receptor
gamma common chain residues SEQ ID NO:1 IQLYQTF (100-106), SEQ
ID NO:3 CLQYLV (161-166), PICGSSQQ (207-214), SEQ ID NO:12
NHEPRFLS (181-188), SEQ ID NO:14 LNLQNL (124-129), SEQ ID NO:16
10　NLSESQL (142-148) and the corresponding sequences from the
human cytokine receptor gamma common chain, i.e. SEQ ID NO: 2
IHLYQTF, SEQ ID NO:4 CLEHLV, SEQ ID NO:11 PLAGSAQH, SEQ ID
NO:13 DYRHKFSL, SEQ ID NO:15 LKLQNL and SEQ ID NO:17 KLSEQL.

　　　　The peptides SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19
15　CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID
NO:26 CPIAGSSQQC, SEQ ID NO:37 CPICGSSQQC, SEQ ID NO:27
CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC,
SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC and SEQ ID NO:32
CLKLQNLC are modeled to mimic the regions of the cytokine
20　receptor gamma common chain predicted to interact with ligands
and the peptides SEQ ID NO:33 CNLSESQLC and SEQ ID NO:34
CKLSESQLC are modeled to mimic the regions of the cytokine
receptor gamma common chain predicted to interact with other
cytokine receptor chains with which the gamma chain forms
25　heterodimers as an active receptor complex.

　　　　According to the invention, the peptides of the
invention inhibit cytokine mediated signaling that involves
cytokine receptors which include the gamma chain. Cytokines
IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 each interact with
30　receptor complexes that include the gamma chain. Accordingly,
the peptides of the invention can be used to inhibit IL-2, IL-
4, IL-7, IL-9, IL-13 and IL-15 signaling. Through this
inhibition, the peptides of the invention are useful to
suppress immunological responses and functions. For example,
35　these cytokines are involved in immunological activity in which
cells are induced to grow, proliferate and/or release factors,

cytokines or other molecules including antibodies. The peptides of the invention can be used to inhibit these activities.

5   Inhibition of T cell and/or B cell proliferation is useful in the treatment of many diseases and conditions including, but not limited to, leukemia, lymphoma, graft versus host disease and other transplant rejections, allergies, asthma and autoimmune and inflammatory diseases such as rheumatoid arthritis, lupus, multiple sclerosis and myasthenia gravis. 10   The peptides of the invention can also inhibit the growth of B cells and T cells and/or inhibit T cells and B cells from releasing substances. Thus, by inhibiting cell growth and/or proliferation and/or function of cells involved in the immune system, the peptides can be useful to suppress the immune 15   system.

The present invention relates to methods of preventing and treating diseases involving or mediated by cells of the immune system. According to some embodiments of the invention, patients are administered compounds of the invention in an 20   amount sufficient to suppress immune function sufficiently to have a therapeutic effect on patients suffering from such diseases involving undesirable function, activity, growth or proliferation of cells of the immune system. According to some embodiments of the invention, patients are administered 25   compounds of the invention in an amount sufficient to suppress immune function sufficiently to have a preventive effect on patients at risk of developing diseases, disorders or conditions involving undesirable function, activity, growth or proliferation of cells of the immune system.

30   **BRIEF DESCRIPTION OF THE FIGURES**

Figures 1A-1D shows data from experiments described in Example 1 testing peptides gamma-4 and gamma-5 of the invention as described in Example 1 to determine their effect on the response of cells to exogenous cytokine IL-2 or IL-4. 35   The cell line used proliferates in the absence of peptide. The data shows that the addition of peptide inhibits cell

proliferation in response to addition of the IL-4 and that such inhibition is dose dependent.

Figure 2 shows data from experiments described in Example 1 testing peptides of the invention as described in
5   Example 1 to determine their effect on the response of cells to exogenous murine IL-4. The cell line used proliferates in the absence of peptide. The data shows that the addition of peptide inhibits cell proliferation in response to addition of mIL-4 and that such inhibition is dose dependent.

10 Figure 3 shows data from experiments described in Example 1 testing peptides of the invention as described in Example 1 to determine their effect on the response of cells to exogenous murine IL-2. The cell line used proliferates in the absence of peptide.

15 Figure 4 shows data from experiments described in Example 1 testing the ability of peptides of the invention as described in Example 1 to inhibit mixed lymphocyte responses (MLR assays as described in Example 2).

Figure 5 shows data from experiments described in
20 Example 1 testing the ability of peptides of the invention as described in Example 1 to inhibit CH12.CX proliferation.

Figures 6A-6F shows data from experiments described in Example 2 testing the ability of peptides of the invention as described in Example 1 to inhibit cytokine mediated activity
25 of various cell lines.

Figure 7 shows data from experiments described in Example 2 testing the ability of peptides of the invention as described in Example 1 to inhibit human IL-4 mediated activity.

Figure 8 shows data from experiments described in
30 Example 2 testing the ability of peptides of the invention as described in Example 1 to inhibit cytokine mediated activity of cells *in vivo*.

DETAILED DESCRIPTION OF THE INVENTION
35 The present invention relates to molecules that have a molecular surface similar to a molecular surface of cytokine receptor common gamma chain. The peptides of the invention

interact with molecules which ordinarily interact with the
gamma chain and result in signal transduction. Not wishing to
bound by any theory, it appears that the peptides of the
invention thereby inhibit signal transduction by inhibiting
5 cytokine:receptor binding either by binding to the cytokine or
by binding to a cytokine receptor chain which forms
heterodimers with the gamma chain in order to form a functional
receptor complex.

According to some embodiments of the present
10 invention, the invention can be represented by the formula:
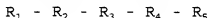
$$R_1 - R_2 - R_3 - R_4 - R_5$$

wherein:

R_1, R_2, R_3, R_4 and R_5 taken together are 5- 25 amino
acids or less and

15 R_1 is a linking moiety, preferably cysteine or
penicillamine;

R_2 is 0-10 amino acids, preferably 0 amino acids;

R_3 is SEQ ID NO:1 IQLYQTF, SEQ ID NO: 2 IHLYQTF, SEQ
ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID NO:5 CLQYLT, SEQ ID
20 NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID NO:8 CLEHLTQ, SEQ ID
NO:9 PIAGSSQQ, SEQ ID NO:10 PLCGSAQH, SEQ ID NO:11 PLAGSAQH,
SEQ ID NO:12 NHEPRFLS, SEQ ID NO:13 DYRHKFSL, SEQ ID NO:14
LNLQNL, SEQ ID NO:15 LKLQNL, SEQ ID NO:16 NLSESQL, SEQ ID NO:17
KLSEQL or such an amino acid sequence with one or more
25 conservative substitutions;

R_4 is 0-10 amino acids, preferably 0 amino acids; and

R_5 is a linking moiety, preferably cysteine or
penicillamine.

It is preferred that R_1 is cysteine or penicillamine.
30 It is more preferred that R_1 is cysteine.

It is preferred that R_2 is 0 amino acids.

It is preferred that R_3 is SEQ ID NO:1 IQLYQTF, SEQ ID
NO: 2 IHLYQTF, SEQ ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID
NO:5 CLQYLT, SEQ ID NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID
35 NO:8 CLEHLTQ, SEQ ID NO:9 PIAGSSQQ, SEQ ID NO:10 PLCGSAQH, SEQ
ID NO:11 PLAGSAQH, SEQ ID NO:12 NHEPRFLS, SEQ ID NO:13

DYRHKFSL, SEQ ID NO:14 LNLQNL, SEQ ID NO:15 LKLQNL, SEQ ID NO:16 NLSESQL or SEQ ID NO:17 KLSEQL.

It is preferred that conservative substititions include I, V, A and L are interchangeable, Q and N are
5 interchangeable, Y and F are interchangeable, S and T are interchangeable and E and D are interchangeable.

It is preferred that R_4 is 0-1 amino acids. It is preferred that R_4 is 0 amino acids.

It is preferred that R_5 is cysteine or penicillamine.
10 It is more preferred that R_5 is cysteine.

In preferred embodiments, the compound is SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19 CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID NO:24 CLQYLTQC, SEQ ID NO:25 CLEHLTQC, SEQ ID NO:26
15 CPIAGSSQQC, SEQ ID NO:27 CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC, SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC, SEQ ID NO:32 CLKLQNLC, SEQ ID NO:33 CNLSESQLC or SEQ ID NO:34 CKLSESQLC.

The present invention provides synthetic peptides that
20 are 5-25 amino acids and comprise amino acid sequences from human or murine cytokine receptor gamma common chain. Non-gamma chain amino acid sequences are provided in some embodiments. The peptides are conformationally restricted, and are generally cyclized. In some embodiments, non-gamma chain
25 sequences are included for the purposes of conformational restriction. In embodiments that comprise both gamma chain and non-gamma chain sequences, at least 20-25% of the amino acid sequence of the peptides of the present invention are derived from he gamma chain. It is preferred that greater than about
30 20-25% of the amino acid sequence of the peptides of the present invention are derived from the gamma chain, more preferably 30-40% and more preferably greater than 50%. In some embodiments, the percentage of amino acid sequence of the peptides of the present invention derived from gamma chain is
35 about 60% or about 75% or more.

The peptides of the present invention may be prepared by any of the following known techniques. Conveniently, the

peptides may be prepared using the solid-phase synthetic
technique initially described in Merrifield (1963) *J. Am. Chem.
Soc.* 15:2149-2154. Other peptide synthesis techniques may be
found, for example, in M. Bodanszky *et al.*, *Peptide Synthesis*,
5 John Wiley & Sons, 2d Ed. (1976); Kent and Clark-Lewis in
Synthetic Peptides in Biology and Medicine, p. 295-358, eds.
Alitalo, K., Partanen, P. and Vakeri, A., Elsevier Science
Publishers, (Amsterdam, 1985); as well as other reference works
known to those skilled in the art. A summary of peptide
10 synthesis techniques may be found in J. Stuart and J.D. Young,
Solid Phase Peptide Synthelia, Pierce Chemical Company,
Rockford, IL (1984). The synthesis of peptides by solution
methods may also be used, as described in *The Proteins*, Vol.
II, 3d Ed., p. 105-237, Neurath, H. et al., Eds., Academic
15 Press, New York, NY (1976). Appropriate protective groups for
use in such syntheses will be found in the above texts, as well
as in J.F.W. McOmie, *Protective Groups in Organic Chemistry*,
Plenum Press, New York, NY (1973).

In general, these synthetic methods involve the
20 sequential addition of one or more amino acid residues or
suitable protected amino acid residues to a growing peptide
chain. Normally, either the amino or carboxyl group of the
first amino acid residue is protected by a suitable,
selectively-removable protecting group. A different,
25 selectively removable protecting group is utilized for amino
acids containing a reactive side group, such as lysine.

Using a solid phase synthesis as an example, the
protected or derivatized amino acid is attached to an inert
solid support through its unprotected carboxyl or amino group.
30 The protecting group of the amino or carboxyl group is then
selectively removed and the next amino acid in the sequence
having the complementary (amino or carboxyl) group suitably
protected is admixed and reacted with the residue already
attached to the solid support. The protecting group of the
35 amino or carboxyl group is then removed from this newly added
amino acid residue, and the next amino acid (suitably
protected) is then added, and so forth. After all the desired

amino acids have been linked in the proper sequence, any
remaining terminal and side group protecting groups (and solid
support) are removed sequentially or concurrently, to provide
the final peptide. The peptide of the invention are preferably
5   devoid of benzylated or methylbenzylated amino acids. Such
protecting group moieties may be used in the course of
synthesis, but they are removed before the peptides are used.
Additional reactions may be necessary, as described elsewhere,
to form intramolecular linkages to restrain conformation.

10   The present peptides may also be prepared by
recombinant DNA techniques, although such methods are not
preferred because of the need for purification and subsequent
chemical modifications to conformationally restrain the
peptides.

15   In addition to peptides which comprise L amino acids,
pharmaceutical compositions according to the present invention
may comprise peptides made up of D amino acids. Because most
enzymes involved in degradation recognize a tetrahedral
alpha-carbon, the D-amino acids were utilized in order to avoid
20   enzyme recognition and subsequent cleavage. Our computer
studies indicate that the same folded presentation of the
peptide is accomplished by reversing the amino acid sequence,
employing D-amino acids. Thus, peptides comprised of D amino
acids are less susceptible to degradation.

25   Conservative substitutions in the amino acid sequence
may be made. Those having ordinary skill in the art can
readily design compounds of the invention with conservative
substitutions for CD8 amino acids. For example, following what
are referred to as Dayhof's rules for amino acid substitution
30   (Dayhof, M.D. (1978) Nat. Biomed. Res. Found., Washington, D.C.
Vol. 5, supp. 3), amino acid residues in a peptide sequence may
be substituted with comparable amino acid residues. Such
substitutions are well known and are based the upon charge and
structural characteristics of each amino acid.

35   Synthesized peptides may be circularized in order to
mimic the geometry of those portions as they occur in the gamma
chain. Circularization may be facilitated by disulfide bridges

between cysteine residues. Alternatively, the peptides may be circularized by means of covalent bonds, such as amide bonds, between amino acid residues of the peptide such as those at or near the amino and carboxy termini.

5   Peptides for use in pharmaceutical compositions of the present invention may be designed following the guidelines set out herein and using well known processes. Methods of synthesizing peptides and circularizing them may be performed routinely using standard techniques and readily available

10   starting materials.

          The present invention relates to methods of therapeutically or prophylactically treating an individual suffering from or susceptible to a disease, condition or disorder associated with T cell or B cell growth, proliferation

15   and/or secretion of biologically active material. The present invention relates to methods of therapeutically or prophylactically treating an individual suffering from or susceptible to a disease, condition or disorder by suppressing immunological responses through the inhibition of cytokine

20   mediated signal transduction.

          Examples of diseases condition and disorders for which the present invention may be employed include T cell and B cell leukemias and lymphomas, inflammatory and autoimmune diseases, allergies and conditions and rejections associated with

25   transplantation protocols.

          Those having ordinary skill in the art can readily identify individuals suspected of suffering from or being susceptible to conditions, diseases and disorders which can be effectively treated or prevented by inhibition of cytokine

30   mediated immune responses effected by the peptides of the invention. Those with ordinary skill in the art could readily identify individuals for whom administration of the compounds of the invention would be beneficial to alleviate or prevent immune responses. Treatment may be provided prophylactically

35   or in response to symptoms associated with undesirable immune responses or activity of cells of the immune system.

Pharmaceutical compositions useful in the methods of the present invention comprise the compounds described herein.

The method of therapeutically or prophylactically treating an individual comprises administering to such an individual an effective amount of a peptide according to the invention. A prophylactically effective amount is an amount which is effective to prevent or decrease the immune response associated with disease condition or disorder to be prevented. A therapeutically effective amount is an amount which is effective to decrease or eliminate symptoms in an individual suffering from such diseases, conditions and disorders. rejection. Those having ordinary skill in the art can readily and routinely determine the ranges of both prophylactically and therapeutically effective amounts of the peptides of the invention without undue experimentation.

The present invention provides pharmaceutical compositions that comprise the peptides of the invention and pharmaceutically acceptable carriers or diluents. The pharmaceutical composition of the present invention may be formulated by one having ordinary skill in the art. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field, which is incorporated herein by reference. In carrying out methods of the present invention, conjugated compounds of the present invention can be used alone or in combination with other diagnostic, therapeutic or additional agents. Such additional agents include excipients such as coloring, stabilizing agents, osmotic agents and antibacterial agents.

For parenteral administration, the peptides of the invention can be, for example, formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The vehicle or lyophilized powder may contain additives that maintain

isotonicity (e.g., sodium chloride, mannitol) and chemical
stability (e.g., buffers and preservatives). The formulation
is sterilized by commonly used techniques. For example, a
parenteral composition suitable for administration by injection
5   is prepared by dissolving 1.5% by weight of active ingredient
in 0.9% sodium chloride solution.

        The pharmaceutical compositions according to the
present invention may be administered as a single dose or in
multiple doses. The pharmaceutical compositions of the present
10 invention may be administered either as individual therapeutic
agents or in combination with other therapeutic agents. The
treatments of the present invention may be combined with
conventional therapies, which may be administered sequentially
or simultaneously. In some embodiments, compounds are
15 administered 1-2 days prior to transplantation, preferably 4-12
hours. Compounds may be delivered during transplantation
procedures. In some embodiments, compounds are administered
for 2 weeks to 2 months after transplantation procedures.

        The pharmaceutical compositions of the present
20 invention may be administered by any means that enables the
active agent to reach the targeted cells. These methods
include, but are not limited to, oral, topical, intradermal,
subcutaneous, intravenous, intramuscular and intraparenteral
modes of administration. The compounds may be administered
25 singly or in combination with other compounds. The compounds
of the invention are preferably administered with a
pharmaceutically acceptable carrier selected on the basis of
the selected route of administration and standard
pharmaceutical practice.

30   The dosage administered varies depending upon factors
such as: pharmacodynamic characteristics; its mode and route
of administration; age, health, and weight of the recipient;
nature and extent of symptoms; kind of concurrent treatment;
and frequency of treatment. Usually, the dosage of peptide can
35 be about 1 to 3000 milligrams per 50 kilograms of body weight;
preferably 10 to 1000 milligrams per 50 kilograms of body
weight; more preferably 25 to 800 milligrams per 50 kilograms

of body weight.   Ordinarily 8 to 800 milligrams are
administered to an individual per day in divided doses 1 to 6
times a day or in sustained release form is effective to obtain
desired results.

5 **EXAMPLES**
Example 1
        Novel peptide mimics that were derived from the
sequence of the cytokine receptor common gamma chain were
designed for the purpose of inhibiting cytokine receptor signal
10 transduction.   Such peptides are capable of inhibiting the
functions of many immune cells which are responsive to these
cytokines and thus are useful in the treatment of various
maladies such as leukemia, lymphoma, inflammatory diseases,
autoimmune disease, transplant rejection, allergies and others.
15   Based on the structural data, 5 sequences (γ1-5) were
identified that are predicted to interact with the ligands of
the γ-chain and one sequence (γ6) that is predicted to interact
with the heterodimeric partner receptors was synthesized.   The
sequences are as follows:

	Murine	Human	% Identity
γ1 (I_{100}->F_{106})	SEQ ID NO:1 IQLYQTF	SEQ ID NO:2 IHLYQTF	86
γ2 (C_{161}->V_{166})	SEQ ID NO:3 CLQYLV	SEQ ID NO:4 CLEHLV	67
γ3 (P_{207}->Q_{214})	SEQ ID NO:36 PICGSSQQ	SEQ ID NO:10 PLCGSAQH	63
γ4 (N_{181}->L_{188})	SEQ ID NO:12 NHEPRFLS	SEQ ID NO:13 DYRHKFSL	50
γ5 (L_{124}->L_{129})	SEQ ID NO:14 LNLQNL	SEQ ID NO:15 LKLQNL	83
γ6 (N_{142}->L_{148})	SEQ ID NO:16 NLSESQL	SEQ ID NO:17 KLSEQL	86

Peptides have been synthesized based on these sequences and cyclized by the addition of cysteine residues at either end and disulfide bridging.   We have tested the following murine peptides in vitro for their ability to inhibit cytokine driven
5 proliferation of cell lines such as CTLL (T-cell) and CH12.CX (B-cell) as well as in MLRs:

Peptide	Sequence
$\gamma 1$ $(I_{100}->F_{106})$	SEQ ID NO:18 CIQLYQTFC
$\gamma 2$ $(C_{161}->V_{166})$	SEQ ID NO:20 CLQYLVC
$\gamma 3$ $(P_{207}->Q_{214})$	SEQ ID NO:26 CPIAGSSQQC
$\gamma 4$ $(N_{181}->L_{188})$	SEQ ID NO:29 CNHEPRFLSC
$\gamma 5$ $(L_{124}->L_{129})$	SEQ ID NO:31 CLNLQNLC
$\gamma 6$ $(N_{142}->L_{148})$	SEQ ID NO:33 CNLSESQLC
$\gamma 2$ lin.	SEQ ID NO:35 ERCLQYLVQY
$\gamma 2T$ $(\gamma 2\ V->T)$	SEQ ID NO:22 CLQYLTC

The murine sequences have been tested in at least two of these proliferation assays. Figures 1A-1D, 2 and 3 show the ability of these peptides to inhibit IL-4 induced proliferation of CTLL's. Figure 4 shows the ability of these peptides to
20 inhibit MLRs and Figure 5 shows the ability of these peptides to inhibit CH12.CX proliferation.
        These data suggest that these peptides can in fact inhibit cytokine responses in vitro. These peptides do not appear to be toxic as the CTLL proliferation to IL-2 is not
25 affected.

Example 2
        Experiments were performed to test the effect of each of peptides gamma-1, gamma-2, gamma-3, gamma-4, gamma-5 and gamma-6 on different cell types using several different
30 assays. The data from the experiments is shown in Figures 6A-6F. The assays were performed as follows:

CTLL Proliferation Assay: The murine IL-2- and IL-4-responsive CTLL cell line was used to assess the ability of the gamma chain peptides to inhibit the binding of these cytokines to their respective receptors. The cell line proliferates in responses to exogenously added cytokine and inhibition of this proliferation by the peptides would be a result of blocking the cytokines from interacting with their receptors. Briefly, 5000 CTLL cells are added to the wells of a 96 well microtitre plate. Either 10 U/ml r-mIL-2 or 1 ng/ml r-mIL-4 are added to these wells along with titred amounts of the indicated peptides. Cultures are incubated at 37°C for 24 hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are deemed the positive response and well containing no peptide and no cytokine are deemed the background (bkg) proliferation. A percent response is calculated as follows: (CPM experimental-CPM bkg)/CPM positive response-CPM bkg). All data are expressed in this manner.

CT4S Proliferation Assay: The murine IL-4 responsive CT4S cell line was used to assess the ability of the gamma chain peptides to inhibit the binding of IL-4 to its receptor. The cell line proliferates in responses to exogenously added mIL-4 and inhibition of this proliferation by the peptides would be a result of blocking the mIL-4 from interacting with their receptors. Briefly, 5000 CT4S cells are added to the wells of a 96 well microtitre plate. r-mIL-4 (50 pg/ml) is added to these wells along with titred amounts of the indicated peptides. Cultures are incubated at 37°C for 48 hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are deemed the positive response and wells containing no peptide and no cytokine are deemed the background (bkg) proliferation. A percent response is calculated as follows: (CPM experimental-CPM bkg)/(CPM positive response-CPM bkg). All data are expressed in this manner.

CH12 Proliferation Assay: The CH12 murine B cell lymphoma, like many lymphomas, is an IL-4 producing cell line

that is also dependent on IL-4 for proliferation. No exogenous
IL-4 is added to the wells of these cultures. Briefly, 1500
cells are added to each well along with titred amounts of the
indicated peptides. Cultures are incubated at 37°C for 48
5   hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate
amount of proliferation. Wells containing no peptide are
deemed the positive response and there is no true background
response. A percent response is calculated as follows: (CPM
experimental)/(CPM positive response). All data are expressed
10 in this manner.

Mixed Lymphocyte Assay: Allogeneic murine mixed
lymphocyte response assays were performed to determine if the
gamma chain peptides were capable of inhibiting this response
as well. Assays were performed as previously described.
15 Briefly, responder lymph node cells were isolated from SJL mice
and stimulator spleen cells were located from (B6xCBA) F_1 mice
responder cells (2 x 10^5/well) were plated in 96 well plates
along with irradiated stimulator cells (4 x 10^5/well). Titred
amounts of gamma chain peptides were added to the indicated
20 wells. Cultures are incubated at 37°C for 3 days and pulsed
with ^{3}H-TdR for the final 18 hours to indicate amount of
proliferation. Wells containing no peptide and both stimulator
and responder cells are deemed the positive response and wells
containing no peptide and no stimulator cells are deemed the
25 background (bkg) proliferation. A percent response is
calculated as follows: (CPM experimental-CPM bkg)/(CPM positive
response-CPM bkg). All data are expressed in this manner.

In vitro testing using human cells and *in vivo* testing
was performed as follows.
30 TF-1 Proliferation Assay: The TF-1 cell line is a
human cell line that is responsive to several cytokine
including human IL-4. Inhibition of IL-4 induced proliferation
of this cell indicates that these peptides are capable if
inhibiting human IL-4. Briefly, TF-1 cells are rested
35 (Cultured in the absence of cytokines) for 48 hours prior to
the initiation of the assay. Cells are plated (20000/well)
along with titred amounts of the indicated peptides and 1 ng/ml

r-hIL-4). Cultures are incubated at 37°C for 48 hours and
pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of
proliferation. Wells containing no peptide are deemed the
positive response and wells containing no peptide and no
5 cytokine are deemed the background (bkg) proliferation. A
percent response is calculated as follows: (CPM experimental-
CPM bkg)/(CPM positive response-CPM bkg). All data are
expressed in this manner. The results are shown in Figure 7.

        Effect of Gamma Chain Peptides *In Vivo*: In order to
10 evaluate the efficacy of these peptides *in vivo*, we challenged
sub-lethally (500Rads) irradiated B10.A mice with 2x10^5 CH12
(B-cell Lymphoma) cells and tracked the lethal effects of this
tumor challenge. Indicated groups of mice (4/group) received
either no treatment, gamma 2T (0.5 mg i.p. on days 0,3,6), of
15 gamma4 (0.5 mg i.p. on days 0,3,6). Data is represented as %
survival. The data is shown on Figure 8.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
    (i) APPLICANT: Townsend, Robert
                           Korngold, Robert
    (ii) TITLE OF INVENTION: Peptide Mimics of the Cytokine Receptor Common Gamma
                               Chain and Methods and Compositions for Making and
                               Using the Same
  (iii) NUMBER OF SEQUENCES: 37
   (iv) CORRESPONDENCE ADDRESS:
       (A) ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & Norris LLP
       (B) STREET: One Liberty Place, 46th Floor
       (C) CITY: Philadelphia
       (D) STATE: Pennsylvania
       (E) COUNTRY: USA
       (F) ZIP: 19103
    (v) COMPUTER READABLE FORM:
       (A) MEDIUM TYPE: Floppy disk
       (B) COMPUTER: IBM PC compatible
       (C) OPERATING SYSTEM: Windows 3.11
       (D) SOFTWARE: Wordperfect for Windows 6.1
   (vi) CURRENT APPLICATION DATA:
       (A) APPLICATION NUMBER:
       (B) FILING DATE:
       (C) CLASSIFICATION:
  (vii) PRIOR APPLICATION DATA:
       (A) APPLICATION NUMBER: US 60/036,941
       (B) FILING DATE: 07-FEB-1997
 (viii) ATTORNEY/AGENT INFORMATION:
       (A) NAME: DeLuca, Mark
       (B) REGISTRATION NUMBER: 33,229
       (C) REFERENCE/DOCKET NUMBER: TJU-2312
   (ix) TELECOMMUNICATION INFORMATION:
       (A) TELEPHONE: 215-568-3100
       (B) TELEFAX: 215-568-3439

(2) INFORMATION FOR SEQ ID NO:1:
    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 7 amino acids
       (B) TYPE: amino acid
       (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ile Gln Leu Tyr Gln Thr Phe
1   5

(2) INFORMATION FOR SEQ ID NO:2:
    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 7 amino acids
       (B) TYPE: amino acid
       (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ile His Leu Tyr Gln Thr Phe
1   5

(2) INFORMATION FOR SEQ ID NO:3:
    (i) SEQUENCE CHARACTERISTICS:
       (A) LENGTH: 6 amino acids
       (B) TYPE: amino acid
       (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Cys Gln Tyr Leu Val
 1   5

(2) INFORMATION FOR SEQ ID NO:4:
     (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 6 amino acids
         (B) TYPE: amino acid
         (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Cys Leu Glu His Leu Val
 1   5

(2) INFORMATION FOR SEQ ID NO:5:
     (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 6 amino acids
         (B) TYPE: amino acid
         (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Cys Leu Gln Tyr Leu Thr
 1   5

(2) INFORMATION FOR SEQ ID NO:6:
     (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 6 amino acids
         (B) TYPE: amino acid
         (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Cys Leu Glu His Leu Thr
 1   5

(2) INFORMATION FOR SEQ ID NO:7:
     (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 7 amino acids
         (B) TYPE: amino acid
         (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Cys Leu Gln Tyr Leu Thr Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:8:

     (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 7 amino acids
         (B) TYPE: amino acid
         (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Cys Leu Glu His Leu Thr Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:9:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Pro Ile Ala Gly Ser Ser Gln Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:10:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Pro Leu Cys Gly Ser Ala Gln His
 1   5

(2) INFORMATION FOR SEQ ID NO:11:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Pro Leu Ala Gly Ser Ala Gln His
 1   5

(2) INFORMATION FOR SEQ ID NO:12:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asn His Glu Pro Arg Phe Leu Ser
 1   5

(2) INFORMATION FOR SEQ ID NO:13:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asp Tyr Arg His Lys Phe Ser Leu
 1   5

(2) INFORMATION FOR SEQ ID NO:14:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both

        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Leu Asn Leu Gln Asn Leu
  1   5

(2) INFORMATION FOR SEQ ID NO:15:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 6 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Leu Lys Leu Gln Asn Leu
  1   5

(2) INFORMATION FOR SEQ ID NO:16:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 7 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asn Leu Ser Glu Ser Gln Leu
  1   5

(2) INFORMATION FOR SEQ ID NO:17:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 7 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Lys Leu Ser Glu Ser Gln Leu
  1   5

(2) INFORMATION FOR SEQ ID NO:18:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 9 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Cys Ile Gln Leu Tyr Gln Thr Phe Cys
  1   5

(2) INFORMATION FOR SEQ ID NO:19:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 9 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: circular
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Cys Ile His Leu Tyr Gln Thr Phe Cys
  1   5

(2) INFORMATION FOR SEQ ID NO:20:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Cys Leu Gln Tyr Leu Val Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:21:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Cys Leu Glu His Leu Val Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:22:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Leu Gln Tyr Leu Thr Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:23:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Cys Leu Glu His Leu Thr Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:24:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Cys Leu Gln Tyr Leu Thr Gln Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:25:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular

    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Cys Leu Glu His Leu Thr Gln Cys
1   5

(2) INFORMATION FOR SEQ ID NO:26:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Pro Ile Ala Gly Ser Ser Gln Gln Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:27:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Cys Pro Leu Cys Gly Ser Ala Gln His Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:28:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Cys Pro Leu Ala Gly Ser Ala Gln His Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:29:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Cys Asn His Glu Pro Arg Phe Leu Ser Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:30:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Cys Asp Tyr Arg His Lys Phe Ser Leu Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:31:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Cys Leu Asn Leu Gln Asn Leu Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:32:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Cys Leu Lys Leu Gln Asn Leu Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:33:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 9 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Cys Asn Leu Ser Glu Ser Gln Leu Cys
1   5

(2) INFORMATION FOR SEQ ID NO:34:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 9 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Cys Lys Leu Ser Glu Ser Gln Leu Cys
1   5

(2) INFORMATION FOR SEQ ID NO:35:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Glu Arg Cys Leu Gln Tyr Leu Val Gln Tyr
1   5   10

(2) INFORMATION FOR SEQ ID NO:36:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Pro Ile Cys Gly Ser Ser Gln Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:37:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Cys Pro Ile Cys Gly Ser Ser Gln Gln Cys
 1   5   10